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Original Research Article

Use of Potentially Harmful Medications and Health-Related Quality of Life among People with Dementia Living in Residential Aged Care Facilities

Pascalle R. Bosboom[a, b] Helman Alfonso[a, b] Osvaldo P. Almeida[a, b, d] Christopher Beer[a–c]

[a]Western Australia Centre for Health and Ageing, Centre for Medical Research, [b]School of Psychiatry and Clinical Neurosciences, and [c]School of Medicine and Pharmacology, University of Western Australia, and [d]Department of Psychiatry, Royal Perth Hospital, Perth, W.A., Australia

Key Words
Quality of Life – Alzheimer's disease questionnaire · Potentially harmful medication · Potentially inappropriate medication · Modified Beers criteria · Drug Burden Index · Polypharmacy

Abstract
Background: Use of potentially harmful medications (PHMs) is common in people with dementia living in Residential Aged Care Facilities (RACFs) and increases the risk of adverse health outcomes. Debate persists as to how PHM use and its association with quality of life should be measured. We designed this study to determine the association of exposure to PHM, operationalized by three different measures, with self-reported Health-Related Quality of Life among people with dementia residing in RACFs. ***Methods:*** Cross-sectional study of 351 people aged >65 years diagnosed with dementia residing in RACFs and with MMSE ≤24. The primary outcome measure was the self-rated Quality of Life – Alzheimer's disease questionnaire (QoL-AD). We collected data on patients' medications, age, gender, MMSE total score, Neuropsychiatric Inventory total score, and comorbidities. Using regression analyses, we calculated crude and adjusted mean differences between groups exposed and not exposed to PHM according to potentially inappropriate medications (PIMs; identified by Modified Beers criteria), Drug Burden Index (DBI) >0 and polypharmacy (i.e. ≥5 medications). ***Results:*** Of 226 participants able to rate their QoL-AD, 56.41% were exposed to at least one PIM, 82.05% to medication contributing to DBI >0, and 91.74% to polypharmacy. Exposure to PIMs was not associated with self-reported

Pascalle R. Bosboom, MA
Western Australia Centre for Health and Ageing (M573)
University of Western Australia
35 Stirling Highway, Crawley, Perth, WA 6009 (Australia)
Tel. +61 8 9224 2855, E-Mail bosboomp@meddent.uwa.edu.au

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QoL-AD ratings, while exposure to DBI >0 and polypharmacy were (also after adjustment); exposure to DBI >0 tripled the odds of lower QoL-AD ratings. ***Conclusion:*** Exposure to PHM, as identified by DBI >0 and by polypharmacy (i.e. ≥5 medications), but not by PIMs (Modified Beers criteria), is inversely associated with self-reported health-related quality of life for people with dementia living in RACFs.

Introduction

The use of potentially harmful medications (PHMs) is common in later life and is associated with an increased risk of unfavourable health outcomes, including adverse drug events, morbidity, mortality and increased healthcare use [1–6]. Use of medication in older age is complicated by several factors, including changes in pharmacokinetics and the presence of multiple comorbidities [7–9]. Consequently, use of PHM is a source of concern that is likely to become more prevalent in the future as the world's population ages [10, 11].

Observational studies have found use of PHM among Australians, with a worryingly high prevalence of the use of antipsychotics, antidepressants, and sedative-hypnotic drugs [12]. In a recent study we also found evidence that people with dementia (PWD) living in Residential Aged Care Facilities (RACFs) in Western Australia continue to be frequently exposed to polypharmacy, prescription of contraindicated medications, antipsychotics, medications with high anticholinergic burden, and combinations of potentially inappropriate medications (PIMs) [13]. These patterns of prescribing are not always in agreement with existing evidence-based guidelines [12, 14, 15]. Thus, there is a pressing need to know more about the epidemiology and sociology of medication use by older adults in Australia that in many cases may be unnecessary, costly and potentially harmful.

Despite its importance, there is still debate as how to identify the use of PHM and several methods or clinical tools have been proposed. A common approach is the use of the Beers criteria [16]. The Beers criteria comprise a list of PIMs that should be avoided altogether, as well as doses, frequencies and duration of other medications that should be avoided in older adults. Use of PIMs has been associated with higher medical costs, increased rates of adverse drug events and poorer health outcomes [16, 17]. A more recently developed tool is the Drug Burden Index (DBI), a measure of total exposure to anticholinergic and sedative medications that incorporates the principle of dose-response and maximal effect [18]. DBI has been independently associated with poorer performances in physical and cognitive function in a population of well-functioning community-dwelling older people in the USA [19]. Similar associations have been reported by Cao et al. [20]. Recently, Gnjidic et al. [21] compared the DBI with the Beers criteria in older adults in low-level residential aged care. They found that the Beers criteria did not predict functional outcome, but the DBI did. Another measure to identify the use of PHM, which could assist healthcare practitioners, is polypharmacy (e.g. quantified as ≥5 medications at one time). Polypharmacy per se also appears to be a risk factor for PIM use and adverse outcomes [22, 23]. However, this apparent relationship may be confounded by the burden of multiple chronic diseases in the older population [24]. Consequently, it is still unclear which of the proposed measures to identify use of PHM best predicts health outcomes of older people.

The use of PHM has been associated with lower quality of life [25], but this area has been thus far neglected. Health-related quality of life (HRQoL) measures have been identified as important multidimensional outcome measures for the treatment of chronic conditions and are increasingly valued to assess the effect of any intervention on recipients' interpretation of outcomes [26–28]. Surprisingly, the potential association of the use of PHM – by different measures – with HRQoL in older adults has only been studied to a limited extent [2, 29].

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Franic and Jiang [2] found that PIM use was not a significant predictor of HRQoL in a cohort of community-dwelling older adults, while polypharmacy was a significant predictor of HRQoL. The latter association was also reported by Henderson et al. [29]. The identification of robust PHM indicators may be useful for clinicians in their decisions on choosing interventions supporting the improvement of HRQoL of PWD living in RACFs.

This study aimed to determine the association between self-reported HRQoL ratings (as measured with a widely used HRQoL measure, the Quality of Life – Alzheimer's disease questionnaire, QoL-AD) of PWD living in RACFs and use of PHM, as identified by three different measures, i.e. the PIMs by Modified Beers criteria, DBI and polypharmacy. We hypothesized that self-reported HRQoL ratings would be inversely associated with the PIMs by Beers criteria, the presence of a DBI (i.e. >0) and polypharmacy (i.e. number of medications ≥5).

Methods

Study Design and Setting

The observational data for this cross-sectional study were obtained from the Dementia in residential care: education intervention trial (DIRECT) conducted by the Western Australia Centre for Health and Ageing. The DIRECT study is a prospective randomised controlled trial of educational interventions aiming to improve QoL of PWD living in RACFs, conducted in the metropolitan area of Perth, Western Australia. All RACFs in the Perth Metropolitan area were sent information (n = 184) regarding the DIRECT study and of those, 36 RACFs agreed to participate. Participating RACFs compiled a list of residents to be screened for study participation. General practitioners (GPs) working at the facility and residents meeting the inclusion criteria were invited to take part. The protocol of this trial has been described in detail elsewhere [30].

Participants

All participants of the DIRECT study (n = 351) were permanent residents of a low-level or high-level RACF, aged ≥65 years, with a clinical diagnosis of dementia and a Mini Mental State Examination (MMSE) total score of ≤24. The exclusion criteria included: (1) subject is identified by facility as medically unstable or as suffering from delirium, or in the terminal stages of a comorbid illness; and (2) subject is unable to participate in assessment instruments in English [30].

The Human Research Ethics Committee at the University of Western Australia approved this study (RA 4/1/1685). All GPs and RACFs provided written agreement to participate. Research staff applied structured written and verbal consent procedures when the residents of the RACFs with cognitive impairment were approached. The assent of the 'next of kin' was required for participation of people with cognitive impairment deemed unable to provide informed consent. This trial was registered (ACTRN12607000417482) on 17/08/2007.

Outcome of Interest

The QoL-AD was the primary outcome measure of this study [31, 32]. The QoL-AD is a short, easy to administer, widely used HRQoL instrument that was designed specifically to assess PWD, with well-established psychometric properties [32, 33]. The scale is composed of 13 items that measure different areas of functioning, selected to reflect relevant areas of the QoL of older adults. Each item offers 4 possible answers that range from 1 ('poor') to 4 ('excellent'), producing a total score where higher scores indicate better QoL. Patient and carer versions are available. The QoL-AD has been modified to produce a 15-item scale

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(maximum score 60) to assess the QoL of PWD living in RACFs according to a standard set of instructions [34, 35].

We have previously shown that QoL-AD ratings of patients and carers show acceptable agreement but are driven by different factors [36], and provide valuable information when used separately, not as a composite score. For this reason we used only the ratings provided by patients in this study (n = 226). Similarly to the study of Bosboom et al. [36], item 7 ('marriage') of the QoL-AD did not apply to this population. For that reason this item was not included in the total score. For further comparison possibilities, we calculated the percentage of the maximum QoL-AD score (%MaxSc) by dividing the total raw score by the number of items and multiplying this figure by 100.

Exposure Variables

Research staff audited participants' clinical records to compile a list of all medicines the participants were prescribed at the time of data collection, either as a regular or pro re nata (PRN or 'as required') medication. Data on all medications was collected, including conventional medications as well as herbal medications, vitamins and minerals. The drug database was cleaned by removing duplicate drugs, correcting spelling errors, and by converting all drugs to generic names. Medications (including all 'as required' medications) were coded according to the World Health Organization Anatomical, Therapeutic, and Chemical Classification System [37]. To identify the use of PHM, the following measures were used:

Firstly, we identified PIMs by the Modified Beers criteria [16]. These definitions and the corresponding data sources have been described elsewhere [1]. Participants taking at least one PIM were classified as exposed to PIM according to the Modified Beers criteria.

Secondly, we calculated the DBI. The DBI is an evidence-based tool that utilizes pharmacologic principles to calculate an individual's total exposure to anticholinergic and sedative medications [18]. The DBI for each participant was calculated as the sum of exposure to each anticholinergic or sedative drug using the equation described by Hilmer et al. [18] and applied by Gnjidic et al. [38, 39]. Participants taking at least one anticholinergic or one sedative medication were classified as exposed to DBI.

Thirdly, we counted the number of medicines for every participant to determine the number of medicines and subsequently the prevalence of participants exposed to polypharmacy, i.e. defined as ≥ 5 medicines [40].

Other Study Measures

We collected demographic and clinical information from participants, including age (in years), gender and prevalent comorbidities. Comorbidity was classified according to the following groups: cardiovascular diseases (including angina, history of heart attack, hypertension), cerebrovascular diseases (including history of stroke), respiratory diseases (including asthma, chronic bronchitis, lung emphysema), heart failure, arthritis or osteoarthritis, other musculoskeletal disorders (including osteoporosis), malignancies, mental health disorders other than dementia (including depression, anxiety), metabolic disorders (including diabetes I or II, thyroid disorders), neurological disorders (including epilepsy) and others (including allergies).

In addition, we assessed participants' cognitive abilities with the MMSE [41] and behavioural and psychological symptoms associated with dementia using the Neuropsychiatric Inventory (NPI) [42], which was rated by staff informants. The NPI total score was calculated by the sum of the frequency rating times the severity rating for all items. Staff informants were required to have known the resident for at least 2 weeks, and to have observed that resident at least 10 times, for a minimum of 1 h in total during the previous 2 weeks.

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Procedures

Research assistants were trained in the standard administration of the assessment tools (including the QoL-AD, MMSE and NPI) and adequate inter-rater reliability was established [43]. In face-to-face interviews, participants (PWD) were handed their own copy of the questionnaire that they could follow, if able to. Participants were able to indicate responses verbally or by circling the response. If a participant was unable to offer responses to more than two items, they were considered unable to complete the measure and their results were excluded from the analyses.

Statistical Methods

This project was originally designed as a hypothesis-driven study. We hypothesized that HRQoL ratings would be inversely associated with the Beers criteria for PIMs, the presence of a DBI (i.e. >0) and polypharmacy (i.e. ≥ 5 medications). Continuous variables were described by their mean and standard deviations, and categorical variables by their count and proportions.

Initially, we treated the primary outcome (QoL-AD %MaxSc) as a continuous variable and, using linear regression modelling, we calculated the crude mean differences between the groups that were exposed to PHM according to the different definitions (i.e. Modified Beers criteria, DBI and polypharmacy). We calculated the adjusted mean differences, firstly adjusted for age, gender, MMSE total score and NPI total score, and later added the number of prevalent morbidities. Trying to identify nonlinear relationships, we subsequently treated the outcome (HRQoL %MaxSc) as a categorical variable by dividing it in tertiles to investigate possible threshold effects, and performed logistic regression to investigate the association between the outcome and the Modified Beers criteria, DBI and polypharmacy. Two models were used: the first contained no adjustments (crude model), the second model was adjusted for age, gender, MMSE total score, NPI total score and number of comorbidities. Results are presented with their associated 95% confidence intervals. We declared as significant alpha values <0.05 and all statistical tests were two-tailed. Data were managed and analysed using the statistical package STATA (version 10, StataCorp, 2009).

Results

Demographic and Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics of the 226 participants that were included in this study. The mean age of the selected participants was 85.9 $\pm$ 7.7 years (range 58–100), 74.8% were women, and the mean MMSE total score was 15.9 $\pm$ 5.9 (interquartile range, IQR, 21–12). The mean NPI total score was 19.8 $\pm$ 23.7 and the mean burden-of-care subscore of the NPI was 6.9 $\pm$ 9.3. The average number of comorbidities was 3.2 $\pm$ 1.6 (range 0–8).

Prevalence of PHM Use

The prevalence of PHM according to the Modified Beers criteria, DBI, and polypharmacy is also presented in table 1.

One hundred and twenty-four participants were exposed to at least one PIM (56.9%); 76 of those 124 used only 1 PIM (61.3%), 41 used 2 PIMs (33.1%) and 7 used 3 PIMs (5.6%). The most common PIMs by Modified Beers criteria in this sample were temazepam (n = 46, 37.1% of the 124 participants exposed to PIM), bisacodyl (n = 12, 9.7%), oxazepam (n = 12, 9.7%), digoxin (n = 11, 8.9%), diazepam (n = 6, 4.8%), dipyridamole (n = 5, 4.0%), and amitriptyline (n = 4, 3.2%).

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Table 1. Demographic and clinical characteristics of the participants (PWD living in RACFs) and the prevalence of use of PHM

Characteristic	PWD in RACFs (n = 226)
Age, years	85.9 ± 7.7
Female sex	169 (74.8)
MMSE	15.9 ± 5.9
NPI	19.8 ± 23.7
NPI burden-of-care subscore	6.9 ± 9.3
Comorbidities	
0	9 (3.9)
1–2	65 (28.8)
3–4	106 (46.9)
5–6	44 (19.5)
7–8	2 (0.9)
PIM(s) by Modified Beers criteria	
0	102 (45.1)
≥1	124 (54.9)
DBI	
0	48 (21.2)
Anticholinergic medication(s)	82 (36.3)
Sedative medication(s)	96 (42.5)
>0	178 (78.8)
Medications	
0	0 (0)
1–2	6 (2.7)
3–4	12 (5.3)
5–6	20 (8.9)
7–8	37 (16.4)
9–10	59 (26.1)
11–12	32 (14.2)
13–14	26 (11.5)
15–16	17 (7.5)
17–18	9 (3.9)
19–20	5 (2.2)
21	3 (1.3)

Values are means ± SD or numbers with percentages in parentheses.

A total of 178 (78.8%) participants were exposed to medications leading to a DBI of >0: 82 participants (46.1%) were taking an anticholinergic medication and 96 (53.9%) were taking sedative medications.

All participants were using at least one medication. A total of 18 of the participants (7.9%) were exposed to 1 to 4 medications at the time of the study; 208 (92.0%) of the participants were identified with polypharmacy (i.e. using ≥ 5 medications at one point in time). The mean number of medications was 10.2 ± 4.04 (median 10, range 1–21).

Association of PHM with HRQoL

The mean QoL-AD total score by self-rating was 41.5 ± 5.9 (range 26–58), corresponding to a mean QoL-AD %MaxSc of 69.2 ± 9.9 (range 43.3–96.7).

Table 2 shows the differences in self-reported QoL-AD ratings according to the use of PHM. The use of ≥1 PIM(s) was not associated with the self-reported QoL-AD in this group of PWD living in RACFs, but both DBI >0 and polypharmacy were, including after adjust-

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www.karger.com/dee

Table 2. Differences in self-reported QoL-AD ratings (i.e. %MaxSc on the QoL-AD) according to exposure to PHM

Measure	No exposure		Exposure		Crude		Adjusted[1]		Adjusted[2]	
	n	mean ± SD	n	mean ± SD	mean difference (95% CI)	p	mean difference (95% CI)	p	mean difference (95% CI)	p
PIM(s) by Beers criteria	102	70.21 ± 10.32	124	68.41 ± 9.51	–1.79 (–4.40 to 0.81)	0.175	–1.68 (–4.04 to 0.68)	0.163	–1.49 (–3.86 to 0.88)	0.217
DBI >0	48	73.02 ± 10.77	178	68.20 ± 9.43	–4.82 (–7.94 to –1.70)	0.003	–4.38 (–7.51 to –1.24)	0.006	–4.07 (–7.25 to –0.89)	0.012
Polypharmacy[3]	18	74.17 ± 10.71	208	68.79 ± 9.74	–5.37 (–10.12 to 0.61)	0.027	–5.54 (–10.26 to –0.82)	0.022	–4.96 (–9.79 to –0.12)	0.045

[1] Adjusted for age, gender, MMSE total score and NPI total score using linear regression modeling. [2] Adjusted for age, gender, MMSE total score, NPI total score and number of comorbidities using linear regression modeling. [3] Number of medications consumed per day ≥5.

Table 3. Odds ratios (95% CI) of self-reported QoL-AD ratings (i.e. %MaxSc on the QoL-AD) according to exposure to PHM

Measure	Tertile QoL-AD %MaxSc[1]	n (n = 226)	Exposed n (%)	Crude			Adjusted[2]		
				OR	95% CI	p	OR	95% CI	p
PIM(s) by Beers criteria	Highest tertile	71	35 (49.3)	1			1		
	Middle tertile	81	46 (56.8)	1.35	(0.71–2.56)	0.356	1.35	(0.70–2.58)	0.370
	Lowest tertile	74	43 (58.1)	1.43	(0.74–2.75)	0.288	1.28	(0.65–2.53)	0.475
DBI >0	Highest tertile	71	46 (64.8)	1			1		
	Middle tertile	81	69 (85.2)	3.13	(1.43–6.84)	0.004	3.47	(1.54–7.83)	0.003
	Lowest tertile	74	63 (85.1)	3.11	(1.39–6.96)	0.006	2.75	(1.18–6.42)	0.019
Polypharmacy (≥5)	Highest tertile	71	62 (87.3)	1			1		
	Middle tertile	81	76 (93.8)	2.21	(0.70–6.92)	0.175	2.43	(0.73–8.10)	0.150
	Lowest tertile	74	70 (94.6)	2.54	(0.75–8.66)	0.136	2.64	(0.71–9.83)	0.148

[1] Tertiles QoL-AD %MaxSc as follows: highest tertile 73.34–96.67; middle tertile 66.517–73.33; lowest tertile 43.33–66.516. [2] Adjusted for age, gender, MMSE total score, NPI total score and number of comorbidities.

ments were made for other measured factors. Similarly, a logistic regression analysis using QoL-AD %MaxSc tertiles showed that DBI >0 tripled the odds of participants being in the middle or lowest tertile of QoL ratings (table 3).

Discussion

Our study indicates that the relevance of PHM in modulating QoL for PWD living in RACFs depends on how this concept is defined. We found that more than half of the PWD living in RACFs were exposed to at least one PIM (by Modified Beers criteria), over 80% were using medications that contributed to a DBI >0, and over 90% were exposed to polypharmacy (i.e. using ≥5 medications). Our data show that QoL ratings were lower in PWD living in RACFs exposed to DBI >0 or polypharmacy.

Interpretation of the results should be considered in light of design of the study. Its cross-sectional nature does not allow us to infer that the use of PHM causes a decline in the QoL of patients, and the possibility of reverse causality (low QoL leading to an increase in the prescription of medications) cannot be ruled out. Secondly, this study only included PWD

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www.karger.com/dee

living in Western Australian RACFs who were aged 65 years or older. Therefore, the findings may not be generalizable to the wider population of older PWD living in the community or in other settings. Thirdly, we did not include data regarding characteristics of the RACFs from where participants were recruited. In addition, the sample of participating RACFs is likely to be subject to volunteer bias, which might have reduced the power of the study to detect relevant associations (type II error). Also, data on depression was partly retrieved from the NPI, but information on insight was not available, and this might have limited our ability to adjust the analyses for these known confounders associated with self-reported QoL [36]. Finally, we did not validate the quality of care provided, which may be an important consideration given that factors such as use of restraints and the incidence of falls may be influenced by facility and staff-related factors [30].

We also acknowledge that we might have introduced a bias by only including PWD living in RACFs who were able to self-rate QoL-AD. Although we have previously shown [30] that the majority of PWD living in RACFs can rate their own QoL (64% in the DIRECT study sample), it needs to be noted that PWD able to self-rate the QoL-AD have higher MMSE (median 17; IQR 12–21) compared with less able people (median 5; IQR 0–11). Therefore, the interpretations of our findings are restricted to PWD with moderate or mild dementia living in RACFs.

Another issue to bear in mind involves the exposure to 'potentially', not 'definitely', harmful medications. Although the risks associated with polypharmacy have been widely reported [22] so are the potential benefits of therapies that lead to cure (e.g. antibiotics) or mitigate distressing symptoms (e.g. pain relief). The development of sound evidence-based strategies that lead to the appropriate use of multiple medications and, at the same time, avoid the undesirable consequences of polypharmacy are urgently needed.

Our study has the merit of having used three different operationalisations to identify the use of PHM in PWD living in RACFs in a moderately large sample (n = 226), which as far as we are aware, has not been done before. Despite its importance, there is still debate as to how to identify the use of PHM and while several methods and clinical tools have been proposed, we are not aware of another study which included simultaneously PIM, DBI and polypharmacy as exposures of interest. In this regard, our study is of clinical relevance and the findings suggest that DBI and polypharmacy can assist healthcare practitioners identify PHM that may compromise the QoL of PWD living in RACFs.

Importantly, the differences that we found were subtle and their clinical relevance uncertain. That is, being exposed to polypharmacy or to drugs contributing to a DBI >0 is associated with 5% lower self-ratings on a widely used HRQoL questionnaire (also after adjustment for possible confounding variables including the number of comorbidities and neuropsychiatric symptoms). At this point, we are unable to state whether such a difference is of immediate or future clinical relevance, but these results suggest a possible intervention opportunity for healthcare practitioners through quality use of medicines.

The prevalence of PIM in our group of participants was high, i.e. more than half of the participants were exposed to ≥1 PIM(s). It was unexpected that use of PIM (by Modified Beers criteria) would not be associated with the self-reported QoL-AD in this group of PWD living in RACFs given that the use of PIMs has been associated with increased rate of adverse drug events and poorer health outcomes [16, 17]. However, our results are consistent with the finding of Franic and Jiang [2], who reported that PIM use was not a significant predictor of HRQoL in a cohort of community-dwelling older adults. Our finding that the use of PIM (by Modified Beers criteria) was not associated with HRQoL while the DBI and polypharmacy were, suggests an advantage of the DBI and polypharmacy over PIMs by Modified Beers criteria as predictors of self-reported HRQoL for this population. Furthermore, the lack of reliable information regarding the dosage of certain medications used by our participants (such

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as hypnotic benzodiazepines) may have led to some misclassification and dilution of the association between PIM and QoL ratings.

The mechanisms that explain the observed association of DBI and polypharmacy with self-rated QoL in this population are uncertain and might be confounded by factors we did not include in our study. It is well known that polypharmacy is a risk factor for adverse health outcomes [22]. But this apparent relationship may be confounded by the burden of multiple chronic diseases [24]. In our study the number of multiple comorbidities did not affect the association between BDI or polypharmacy with HRQoL. A similar comparison could be made for the possible influence of neuropsychiatric symptoms, which one might expect to increase the risk of exposure to medications, but adjustment for this (with the NPI) had no obvious effect on the association between HRQoL and DBI or polypharmacy. The longitudinal implications of our findings should be explored by future studies.

In conclusion, use of PHM is common and is inversely associated with the self-reported HRQoL in PWD living in RACFs. With regards to clinical tools, our data suggest that DBI and polypharmacy may be better predictors of HRQoL than PIMs by Modified Beers criteria. This study supports the recommendation that, with the overall aim of improving QoL as outcome of care for PWD in RACFs, efforts should be made to avoid the use of PHM through quality use of medicine initiatives.

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Disclosure Statement

There is no conflict of interest.

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